General

Guideline Title

Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Sep. 57 p. (Diagnostics guidance; no. 10).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Oncotype DX is recommended as an option for guiding adjuvant chemotherapy decisions for people with oestrogen receptor positive (ER+), lymph node negative (LN−) and human epidermal growth factor receptor 2 negative (HER2−) early breast cancer if*:

- The person is assessed as being at intermediate risk and
- Information on the biological features of the cancer provided by Oncotype DX is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy and
- The manufacturer provides Oncotype DX to National Health Service (NHS) organisations according to the confidential arrangement agreed with the National Institute for Health and Care Excellence (NICE).

NICE encourages further data collection on the use of Oncotype DX in the NHS (see Section 7 in the original guideline document).

MammaPrint, IHC4 and Mammostrat are only recommended for use in research in people with ER+, LN− and HER2− early breast cancer, to collect evidence about potentially important clinical outcomes and to determine the ability of the tests to predict the benefit of chemotherapy (see section 7 of the original guideline document). The tests are not recommended for general use in these people because of uncertainty about their overall clinical benefit and consequently their cost effectiveness.

*The analysis leading to this recommendation was based on intermediate risk of distant recurrence being defined as a Nottingham Prognostic Index (NPI) score above 3.4. It is anticipated that an NPI score can be simply calculated from information that is routinely collected about people with breast cancer. Other decision-making tools or protocols are also currently used in the NHS and these may also be used to identify people at intermediate risk.

Clinical Algorithm(s)

An algorithm titled "Diagnosis and Management Pathway in Breast Cancer" is provided in the original guideline document.

Scope

Disease/Condition(s)

Early breast cancer

Guideline Category

Evaluation

Management

Risk Assessment

Technology Assessment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Medical Genetics

Obstetrics and Gynecology

Oncology

Pathology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To determine whether using gene expression profiling and expanded immunohistochemistry tests (MammaPrint, Oncotype DX, IHC4 and Mammostrat), in conjunction with current decision-making protocols (including tools such as the Nottingham Prognostic Index [NPI] and Adjuvant! Online) to guide the use of adjuvant chemotherapy, cost-effectively improves health outcomes and quality of life of people with early stage breast cancer, compared with current decision-making protocols alone

Target Population

Patients with early breast cancer

Interventions and Practices Considered

Gene expression profiling (MammaPrint and Oncotype DX) and expanded immunohistochemistry tests (IHC4 and Mammostrat)

Major Outcomes Considered

- Analytical validity of the tests (repeatability and reproducibility)
- Clinical validity (prognostic ability or the degree to which the test can accurately predict the risk of an outcome)
- Clinical utility
    - Reclassification of risk compared with existing prognostic variable
    - Impact of the test results on clinical decision making
    - Predictive ability of the test
    - Quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Methods for Reviewing Effectiveness

Background Context

The present review evaluates nine prognostic tests for guiding chemotherapy treatment decisions in early stage breast cancer.

For two of the nine tests (Oncotype DX and MammaPrint), the current review updates an existing systematic review of gene expression profiling tests for breast cancer. Two previous systematic reviews (one an update of the other) reviewed the literature relating to both Oncotype DX and MammaPrint. In the first review, the authors conducted an exhaustive literature review of various electronic databases (covering biomedical literature) between 1990 and 2006. Additional sources included the grey literature (conference proceedings), hand searching the reference list of included studies and pertinent reviews and by contacting the manufacturers of the two tests, regulatory authorities and querying experts in the field. In the second review, the authors updated the first review by updating the search strategy to include all relevant available literature between January 2007 to December 2009.

In the present review, new search strategies were developed for all of the nine tests based on scoping searches (and strategies reported in the two existing systematic reviews for the Oncotype DX and MammaPrint test).

Identification of Studies

Electronic Databases

Studies were identified by searching the following electronic databases:

- MEDLINE (via Ovid SP) 1950 to May 2011
- MEDLINE In-Process & Other Non-Indexed Citations (via Ovid SP) 1950 to May 2011
- EMBASE (via Ovid SP) 1980 to May 2011
- Cochrane Central Register of Controlled Trials (CENTRAL) (via Cochrane Library Issue 3, 2011)
- Cochrane Database of Systematic Reviews (CDSR) (via Cochrane Library Issue 8, 2011)
- National Health Service (NHS) Database of Abstracts of Reviews of Effectiveness (DARE) (via Cochrane Library Issue 3, 2011)
- Health Technology Assessment Database (HTA) (via Cochrane Library Issue 3, 2011)
- BIOSIS previews (via Ovid SP) 1926 to May 2011
- Web of Science (WoS) (includes Science Citation Index and Conference Proceedings Citation Index) (via WOK) 1899 to May 2011

Extensive searches were undertaken to identify all literature relating to the clinical effectiveness of gene expression profiling (GEP) and expanded immunohistochemistry (IHC) tests to guide use of chemotherapy in breast cancer management. Sensitive keyword strategies using free text and where available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition (e.g., breast cancer) were combined with synonyms related to the test (e.g., MammaPrint, OncotypeDX, Randox Breast Cancer Array [BCA], BluePrint, PAM50, Breast Cancer Index, IHC4, Nottingham Prognostic Index plus [NPI+]).

Searches were not restricted by publication type or language. However, all searches were limited by date. For the Oncotype DX and MammaPrint test, the searches were restricted to January 2009 to the present (May 2011) as the search strategies from the existing systematic reviews appear to be of good quality and clearly reported and as a result all studies prior to 2009 would have been identified. For the remaining seven tests, the searches were restricted to January 2002 to the present (May 2011). The first evidence for the GEP and expanded IHC tests was reported in 2002 for Oncotype DX and MammaPrint. As these are the most established test and furthest along the validation pathway, evidence for subsequent tests will not predate this. An example of the MEDLINE search strategy is provided in Appendix 1 in the DAR (see the "Availability of Companion Documents" field).

Other Resources

To identify additional published, unpublished and ongoing studies, the reference lists of all relevant studies (including existing systematic reviews) and information received by the manufacturers were hand-searched and key experts in the field were contacted.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software version 12.0.

Inclusion and Exclusion Criteria

The inclusion of potentially relevant articles was undertaken using a two-stage process. First, one experienced systematic reviewer screened all titles and abstracts and excluded any citations that clearly did not meet the inclusion criteria. Second, the full manuscripts of all potentially eligible articles were assessed for inclusion. At each step, articles which did not satisfy the inclusion criteria were excluded. Any uncertainties in the selection process were resolved through discussion with a second reviewer. The relevance of each article for the clinical effectiveness review was assessed according to the criteria listed in Section 4.1.3 in the DAR.

Economic Analysis

Systematic Review of Existing Cost-effectiveness Evidence

Methods

A systematic search of the existing literature evaluating the cost-effectiveness of the nine GEP and expanded IHC tests identified by NICE (Oncotype DX, MammaPrint, Mammostrat, PAM50, Blueprint in combination with MammaPrint, IHC4, Randox Breast Cancer Array, Breast Cancer Index – BCI, and NPI+) to guide the adjuvant chemotherapy treatment decision in the management of early breast cancer was undertaken. Only full economic evaluations published in English addressing the cost-effectiveness of those tests compared with the Nottingham Prognostic Index (NPI), Adjuvant! Online or any adaptations of these tools in clinical practice were included in the review. Cost-effectiveness studies that used Sankt (St.) Gallen, the National Comprehensive Cancer Network (NCCN), and National Institutes of Health (NIH) guidelines were excluded from the review, due to time and resource constraints, as these comparators are not directly relevant to the UK context, but such

studies were scanned by the reviewers to inform the model development.

Seven databases were searched for relevant published literature including MEDLINE; Medline in process (Ovid); CINAHL; EMBASE; NHS EED and HTA databases (via the Cochrane Library); Web of Science (which includes the Science Citation Index (SCI) and BIOSIS. In addition, literature searches were undertaken for the clinical effectiveness review, and relevant cost papers were identified from these searches. In addition, the reference lists of relevant articles were hand searched. Full details of the search strategies used in MEDLINE are presented in Appendix 1 of the DAR (see the "Availability of Companion Documents" field) (these have been adapted for use in other databases). Searches were not restricted by language.

Studies were selected for inclusion through a two-stage process. Titles and abstracts were examined for inclusion by one reviewer. Full manuscripts of selected citations were then retrieved and assessed by the same reviewer.

Number of Source Documents

Assessment of Clinical Effectiveness

Overview of Existing Systematic Reviews of the Oncotype DX and MammaPrint Tests

In total, 21 studies on the Oncotype DX and 13 on the MammaPrint test were identified and included by the authors of these reviews. A summary of the evidence type and overall quality of each study is provided, if reported, in Table 8 and Table 9 in the Diagnostics Assessment Report (DAR) (see the "Availability of Companion Documents" field).

Studies Included in the Current Systematic Review

The literature searches identified 5993 potentially relevant citations. Of the title and abstracts screened 218 relevant full papers or abstracts were retrieved and assessed for inclusion. A total of 32 citations evaluating the effectiveness of nine prognostic tests (for guiding chemotherapy treatment decisions in early stage breast cancer) met the inclusion criteria.

See Figure 2 in the DAR for a flow chart describing the process of identifying relevant literature. See also Appendix 6 in the DAR (see the "Availability of Companion Documents" field) for information on studies excluded from the review.

Economic Analysis

The search retrieved 72 citations relating to cost effectiveness and two additional references were known by the author. Fifty-six articles were excluded at title stage, and four articles were excluded at abstract level. Thirteen studies (corresponding to 14 references) were examined at full-text level and four studies (corresponding to five references) were identified as meeting the inclusion criteria of the systematic review of economic evaluations. Of the four identified economic studies (corresponding to five references), two economic evaluations compared MammaPrint against Adjuvant! Online and two economic evaluations compared Oncotype DX against Adjuvant! Online. None of the four published economic evaluations were conducted in a UK setting.

The manufacturers submitted 2 economic models (one comparing the use of Oncotype DX with current clinical practice in the UK and the other comparing the cost-effectiveness of treatment guided using Mammostrat with treatment guided using Nottingham Prognostic Index [NPI] in women with early breast cancer, estrogen positive [ER+], lymph node negative [LN-] in the UK).

The External Assessment Group submitted an independent economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Methods for Reviewing Effectiveness

Data Abstraction Strategy

Data abstraction was performed by one reviewer into a standardised data extraction form and independently checked for accuracy by another reviewer. Discrepancies were resolved by discussion and if disagreement could not be reached a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Where appropriate, the authors of the studies (or the manufacturer/sponsor of the test) were contacted to provide further details in cases where information was missing from the articles.

Critical Appraisal Strategy

The methodological quality of each included study was assessed by one reviewer and independently checked by another reviewer using the criteria recommended by Altman (2001) for assessing the internal validity of articles dealing with prognosis. Any discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Blinding of the quality assessor to author, institution, or journal was not considered necessary. The quality assessment items recommended by Altman employed six dimensions relating to the risks of bias of prognostic studies and included the following: sample of participants, follow up of participants, outcome, prognostic variable, analysis and treatment subsequent to inclusion in cohort. Study quality was assessed with each item scored as "yes", "no", or "unclear". Where a study was reported in more than one publication, its quality was assessed on the basis of the combined data from all relevant publications. Further details on the methodological assessment tool is provided in Appendix 2 in the DAR (see the "Availability of Companion Documents" field).

As the current review updates two existing systematic reviews of gene expression profiling tests for breast cancer (Oncotype DX and MammaPrint test), the methodological quality of these two systematic reviews was assessed using the criteria recommended by Shea et al. The quality assessment criteria for assessing systematic reviews included items on *a priori* design, data extraction, literature searching, quality assessment, data synthesis, publication bias and conflicts of interest. Further details on the methodological assessment tool together with the detail of the assessment of each review are provided in Appendix 3 in the DAR (see the "Availability of Companion Documents" field).

Methods of Data Synthesis

Studies which met the review's entry criteria were eligible for inclusion in meta-analyses if this was appropriate in terms of comparability of the study populations, outcomes and diagnostic thresholds, and if the studies were unlikely to be biased. However, because of the degree of heterogeneity, meta-analysis was not considered appropriate. The presentation of results is therefore limited to a narrative review.

Economic Analysis

Independent Economic Assessment - Methods

The key objective of the economic assessment is to address the cost-effectiveness of the use of gene expression profiling (GEP) and expanded immunohistochemistry (IHC) tests to guide adjuvant chemotherapy decision-making in women with early breast cancer in England and Wales. Only two of the tests, Oncotype DX and MammaPrint, have published evidence about the economic value of the test to date but are not UK specific. Two UK economic evaluations were submitted by the manufacturers of these tests as part of the NICE process of request for additional information to the manufacturers. The review of the published cost-effectiveness evidence and the critique of the economic evaluations submitted by the manufacturers for this appraisal showed a number of limitations that need to be addressed. Therefore, a *de novo* economic model was constructed to address these limitations, where possible, and to estimate the cost-effectiveness of a wider range of GEP and expanded IHC tests. Notably, the External Assessment Group (EAG) economic assessment uses UK specific data and addresses the following limitations on the proportion of patients that currently receive chemotherapy in England and Wales, the risk of distant recurrence in a UK population, a subgroup

analysis offering the test to patients that are the most likely to benefit from the test and a more accurate estimation of the cost of chemotherapy in England and Wales.

The economic model takes into account the selection of patients to receive chemotherapy with the new tests compared with current practice, alongside evidence of the reduction in the risk of relapses (and subsequent deaths) associated with adjuvant chemotherapy. It also takes into account the costs and reduction in quality of life resulting from the adverse events associated with the chemotherapy.

Description of the de novo Economic Model

Overview

A probabilistic decision analytic model was developed to estimate the costs and quality-adjusted life years (QALYs) of adjuvant chemotherapy guided by GEP and expanded IHC tests compared to the current clinical practice in England and Wales (using cancer registry data). The economic model was programmed using MS Excel® software (MS Excel 2011) and used a 6 monthly cycle length and followed patients over a lifetime horizon (100 years as upper age limit) in the base case. Shorter horizons were examined in sensitivity analyses. In accordance with the NICE's interim methods guide for diagnostics, the economic model adopted the perspective of the UK NHS and personal social services (PSS) with costs and benefits discounted at 3.5% per annum.

Four tests were selected for the economic evaluation (Oncotype DX, IHC4, MammaPrint and Mammostrat). However, the level and quality of evidence supporting each of the tests is different. Three separate analyses were performed using the best direct sources of data available for each test and these should not be directly compared. This was done because the EAG considered that combining evidence from different studies, based on different methodologies and with different patient characteristics limited the conclusions that could be drawn from the analyses and, in particular, the comparisons that could be made between the analyses.

The primary analysis compared current clinical practice with the adjuvant treatment decision based on the addition of Oncotype DX to current clinical practice and the addition of IHC4 to current clinical practice. Two exploratory analyses were undertaken to compare current clinical practice with the addition of MammaPrint and Mammostrat to current clinical practice. These analyses were considered to be exploratory only due to significant limitations in the evidence base.

Model Structure

The model takes into account the reduction in the risk of relapses (and subsequent deaths) associated with the use of adjuvant chemotherapy. It also takes into account the costs and reduction in quality of life resulting from the adverse events associated with the chemotherapy.

All patients in the model are assumed to receive endocrine therapy. A proportion of patients in the comparator arm (current practice) received chemotherapy, based on cancer registry data. In the intervention arm (addition of new test) patients were assigned into a risk category using the new test and this additional information influenced the decision to prescribe chemotherapy. The economic model comprises three key components:

1. Firstly, patients were assigned to risk categories according to the assigned risk score/group using the new test.
2. Secondly, women that would receive chemotherapy, as well as endocrine therapy, were identified, using the additional knowledge of the assigned risk group.
3. Thirdly, the natural history of breast cancer for patients treated with endocrine therapy alone or with the addition of chemotherapy was then simulated using a state transition model.

See Section 5 in the DAR for additional detailed information on economic analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Developing Recommendations

After reviewing the evidence the Diagnostic Advisory Committee (DAC) agrees draft recommendations on the use of the technology in the National Health Service (NHS) in England. When formulating these recommendations, the Committee has discretion to consider those factors it believes are most appropriate to the evaluation. In doing so, the Committee has regard to any relevant provisions of the National Institute for

Health and Care Excellence's (NICE's) Directions, set out by the Secretary of State for Health, and legislation on human rights, discrimination and equality. In undertaking evaluations of healthcare technologies, NICE takes into account the broad balance of clinical benefits and costs, the degree of clinical need of patients under consideration, any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of NICE by the Secretary of State, and any guidance issued by the Secretary of State, and the potential for long-term benefits to the NHS of innovation.

The Committee takes into account advice from NICE on the approach it should take to making scientific and social value judgements. Advice on social value judgements is informed in part by the work of NICE's Citizens Council.

The Committee takes into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: race, gender, disability, religion or belief, sexual orientation, gender reassignment and pregnancy or maternity.

The Committee considers the application of other Board-approved NICE methods policies, such as the supplementary guidance on discounting and the end-of-life criteria, if they are relevant to the evaluation.

Because the Programme often evaluates new technologies that have a thin evidence base, in formulating its recommendations the Committee balances the quality and quantity of evidence with the expected value of the technology to the NHS and the public.

The credibility of the guidance produced by NICE depends on the transparency of the DAC's decision-making process. It is crucial that the DAC's decisions are explained clearly, and that the contributions of registered stakeholders and the views of members of the public are considered. The reasoning behind the Committee's recommendations is explained, with reference to the factors that have been taken into account.

The language and style used in the documents produced by the Committee are governed by the following principles:

- Clarity is essential in explaining how the DAC has come to its conclusions.
- The text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This needs careful judgement so that enough information and justification is given in the recommendations to enable the reader to understand what evidence the DAC considered and, if appropriate, who provided that evidence.

The Committee may take into account factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the reference-case cost analysis, such as improved processes.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Oncotype DX and IHC4

Tests used for all women with oestrogen receptor positive (ER+), lymph node negative (LN−), human epidermal growth factor receptor 2 negative (HER2−) early breast cancer in England and Oncotype DX is assessed at the list price of £2580. Table 1 in the original guideline document shows per-patient costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) in the primary economic analysis (Oncotype DX and IHC4 compared with current practice).

Compared with current practice, Oncotype DX was associated with an incremental cost of £2575 and incremental QALYs of 0.1, yielding an ICER of £26,940 per QALY gained. IHC4 was £179 cheaper than current practice (cost saving), with incremental QALYs of 0.05 and was predicted to be dominant (that is, provide more QALYs at a lower cost) compared with current clinical practice. Oncotype DX, IHC4 and current practice were also compared using incremental analysis; that is, the least effective strategy was compared with the next least effective strategy that was neither dominated nor extendedly dominated. The cost-effectiveness acceptability curve showed that the probability of IHC4 being cost-effective (when compared with current practice) was almost 100% if the maximum acceptable ICER was £20,000 per QALY gained. At the same maximum acceptable ICER, the probability of Oncotype DX being cost-effective, when compared with current practice only, was 12.4%.

Tests used for women with ER+, LN−, HER2− early breast cancer and an Nottingham Prognostic Index (NPI) score above 3.4, and Oncotype DX is assessed at the list price of £2580. Table 2 of the original guideline document shows per patient costs, QALYs and ICERs in the primary

economic analysis (Oncotype DX and IHC4 compared with current practice).

Compared with current practice, Oncotype DX was associated with an incremental cost of £2095 and incremental QALYs of 0.23, which resulted in an ICER of £9007 per QALY gained. IHC4 was £498 cheaper than current practice (cost saving), with incremental QALYs of 0.14 and was predicted to be dominant (that is, provide more QALYs at a lower cost) compared with current clinical practice. Oncotype DX, IHC4 and current practice were also compared using incremental analysis; that is, the least effective strategy was compared with the next least effective strategy that was neither dominated nor extendedly dominated. The cost-effectiveness acceptability curve showed that the probability of IHC4 being cost effective (when compared with current practice) was almost 100% if the maximum acceptable ICER was £20,000 per QALY gained. At the same threshold, the probability of Oncotype DX being cost-effective, when compared with current practice only, was 91.6%.

Mammostrat (Exploratory Analysis)

Test Used for All Women with ER+, LN−, HER2− Early Breast Cancer

The proportion of patients receiving chemotherapy increased with the use of Mammostrat when compared with current practice (21.16% and 14.42% respectively). Current practice was associated with a mean cost of £7699 and mean QALYs of 12.86. Mammostrat was associated with a mean cost of £9040 and mean QALYs of 12.91. The ICER for Mammostrat was estimated to be £26,598 per QALY gained. However, there were significant uncertainties and limitations associated with this analysis. The cost-effectiveness acceptability curve showed a 36.0% probability of Mammostrat being cost effective if the maximum acceptable ICER is £20,000.

Tests Used for Women with ER+, LN−, HER2− Early Breast Cancer and a NPI Score above 3.4

The proportion of patients receiving chemotherapy increased slightly with the use of Mammostrat when compared with current practice (34.27% and 33.60% respectively). Current practice was associated with a mean cost of £9717 and mean QALYs of 12.34. Mammostrat was associated with a mean cost of £10,985 and mean QALYs of 12.29. Mammostrat was shown to be dominated by current practice. The cost-effectiveness acceptability curve showed an 18.0% probability of Mammostrat being cost-effective if the maximum acceptable ICER is £20,000.

MammaPrint (Exploratory Analysis)

Test Used for All Women with ER+, LN−, HER2− Early Breast Cancer

The proportion of patients receiving chemotherapy increased with the use of MammaPrint when compared with current practice (44.18% and 14.42% respectively). Current practice was associated with mean costs of between £6408 and £6629, and mean QALYs of between 13.39 and 13.49. MammaPrint was associated with mean costs of between £10,017 and £10,748 and mean QALYs of between 13.47 and 13.78. Because of uncertainty around the evidence on the benefit of chemotherapy for the MammaPrint risk groups, the results for MammaPrint were presented as a range (based on the confidence interval for the benefit of chemotherapy). The ICER was estimated to be between £12,240 and £53,058 per QALY gained. Additional uncertainties include the lack of UK data in a relevant population (patients with ER+, LN−, HER2− breast cancer; particularly in relation to risk reclassification compared with UK practice), the impact of the test on clinical decision-making in the UK and reliance on data mainly from pre-menopausal populations.

Tests Used for Women with ER+, LN−, HER2− Early Breast Cancer and a NPI Score above 3.4

The proportion of patients receiving chemotherapy increased with the use of MammaPrint when compared with current practice (90.31% and 33.60% respectively). Current practice was associated with mean costs of between £8281 and £8872 and mean QALYs of between 12.81 and 13.07. MammaPrint was associated with mean costs of between £12,278 and £14,014 and mean QALYs of between 12.99 and 13.73. Because of uncertainty around the evidence on the benefit of chemotherapy for the MammaPrint risk groups, the results for MammaPrint were presented as a range (based on the confidence interval for the benefit of chemotherapy). The ICER for MammaPrint was estimated to be between £6053 and £29,569 per QALY gained. Additional uncertainties include the lack of UK data and the reliance on data mainly from pre-menopausal populations.

See Sections 5 and 6 in the original guideline document for more information on cost analysis.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The National Institute for Health and Care Excellence (NICE) sends the Diagnostics Assessment Report (DAR), with any confidential material removed, to registered stakeholders for comment. Stakeholders have 10 working days to return comments. Models supporting the DAR are made available to registered stakeholders on request during this period.

NICE presents anonymised registered stakeholder comments on the DAR, along with any responses from NICE or the External Assessment Group (EAG), to the Committee and later publishes these comments on its website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Diagnostics Advisory Committee considered clinical and cost-effectiveness evidence from a systematic review of gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management prepared by an External Review Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Gene expression profiling (GEP) and expanded immunohistochemistry (IHC) (or protein expression) tests aim to improve the targeting of chemotherapy in breast cancer by improving the stratification and identification of patients who will gain most benefit from chemotherapy. This is based on the knowledge that certain biological features of cancers may indicate an increased likelihood of rapid growth and metastatic potential.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Clinical Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The National Institute of Health and Care Excellence (NICE) will support this guidance with a range of activities to promote the

recommendations for further research. This will include incorporating the research recommendations in Section 7 in the original guideline document into the NICE guidance research recommendations database (available on the NICE website at www.nice.org.uk) and highlighting these recommendations to public research bodies. The research proposed will also be put forward to NICE's Medical Technologies Evaluation Programme research facilitation team for consideration of the development of specific research protocols.

- The manufacturer has offered Oncotype DX to the National Health Service (NHS) under a proposal (December 2012) that makes Oncotype DX available to the NHS at a revised price. The proposal price is commercial-in-confidence. It is the responsibility of the manufacturer to communicate details of the proposal to the relevant NHS organisations.

Implementation Tools

Clinical Algorithm

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Sep. 57 p. (Diagnostics guidance; no. 10).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Sep

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Diagnostics Advisory Committee

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Financial Disclosures/Conflicts of Interest

Committee members are required to submit a declaration of interests on appointment, in every year of their tenure, and at each Committee meeting, in line with the National Institute for Health and Care Excellence's (NICE's) code of practice for declaring and dealing with conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download as a Kindle or EPUB ebook from the NICE Web site.

Availability of Companion Documents

The following are available:

- Ward S, Scope A, Rafia R, Pandor A, Harnan S, Evans P. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management. Diagnostics assessment report. Sheffield (UK): School of Health and Related Research (ScHARR), University of Sheffield; 2011 Oct. 279 p. Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site.
- Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management. Diagnostics assessment report appendices. Sheffield (UK): School of Health and Related Research (ScHARR), University of Sheffield; 2011 Oct. 85 p. Electronic copies: Available from the NICE Web site.
- Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. Costing template. London (UK): National Institute for Health and Care Excellence; 2013 Sep. Electronic copies: Available from the NICE Web site.
- Diagnostics Assessment Programme manual. London (UK): National Institute for Health and Care Excellence; 2011 Dec. 130 p. Electronic copies: Available from the NICE Web site.

Patient Resources

The following is available:

- Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat: information for the public. National Institute for Health and Care Excellence (NICE); 2013 Sep. (Diagnostics guidance; no. 10). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site.

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